UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,981	03/22/2001	Gary DeJong	24601-416B	7622

24961 7590 09/30/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
4350 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122-1246

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	22

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,981	DEJONG ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a reply to the amendment filed 16 June 2003 (Paper No. 21). In response to the Office Action mailed 16 December 2003 (Paper No. 19). Claims 1-16 and 30 were considered in Paper No. 19. Claims 1, 3, 9, 10, 16 and 30 were amended in Paper No. 21. Claims 1-16 and 30 are pending and under consideration.

Response to Amendment

Claim Objections

Objection to claims 1, 3 and 30 as informal is withdrawn.

Double Patenting

Claims 1-16 and 30 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-8, 11-16 and 30 of copending Application No. 10/086,745. Applicant's statement regarding cancellation of the conflicting claims in the 10/086,745 application upon receipt of an Office Action in that case is acknowledged. However, until such time as the claims are actually canceled, the instant double patenting rejection will stand.

Claim Rejections - 35 USC § 112

Claims 1-4, 6-16 and 30 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record and herein below in the response to arguments.

Rejection of claim 5 under 35 U.S.C. §112, first paragraph, as lacking enablement is withdrawn.

Rejection of claim 9 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Claim Rejections - 35 USC § 102

Rejection, under 35 U.S.C. 102(b), of claims 1, 2, 4, 6-10, 12, 14-16 and 30 as anticipated by Felgner *et al.*, claims 1, 2, 4, 6, 7, 9, 10, 12 14-16 and 30 as anticipated by Neves *et al.* and claims 1, 2, 4, 6, 8-10, 12 14-16 and 30 as anticipated by Zelphati *et al.* is withdrawn in view of the limitation of the claims to introducing a "large nucleic acid molecule", which is defined as being at least about 0.5 Mbase pairs (specification, sentence bridging pages 9-10).

Claim Rejections - 35 USC § 103

Claims 1-4 and 11-15 stand rejected under 35 U.S.C. 103(a) as unpatentable over either one of Felgner *et al.* (*supra*) or Zelphati *et al.* (*Supra*) in view of Nolan *et al.* (2000) WO 00/34436 for reasons of record and herein below in the response to arguments.

Please note that, although the rejection was not set forth against claims 4, 14 and 15 in the previous office action, this is clearly the result of a typographical error as all of the references teach an nucleic acid that is DNA according to claim 4 and an animal cell according to claims 14 and 15.

Response to Arguments

Declaration under 37 C.F.R. §1.132

The declaration by Sandra Vanderbyl has been fully considered and is found to adequately demonstrate that the methods disclosed in the specification are enabling for a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising introducing a large nucleic acid molecule metabolically labeled with bromodeoxyuridine or iododeoxyuridine into cells, detecting labeled cells and measuring the product of a reporter gene encoded by the nucleic acid. However, claims 1-16 and 30 are not limited to the method disclosed in the declaration; therefore, the showings of the declaration fail to demonstrate enablement for the full scope of the claimed subject matter. The declaration provides detailed description of a single embodiment of the claimed invention wherein artificial chromosomes are labeled by culturing a cell line containing the artificial chromosomes in a medium containing iododeoxyuridine or bromodeoxyuridine. The labeled artificial chromosomes were isolated from the cells and introduced into another cell line by transfection. The percentage of transfected cells was determined using an anti-iododeoxyuridine antibody, and expression of the GFP reporter gene was determined by flow cytometry. The results obtained demonstrate that artificial chromosomes labeled *in situ* with bromodeoxyuridine or iododeoxyuridine remain competent to express a reporter gene. However, the teachings in the Declaration address only a single embodiment of the claimed invention, which encompasses many different labels and methods of labeling DNA. For the reasons provided herein below in the response to arguments, the Declaration fails to show that the skilled artisan would be able to practice the full scope of the claimed invention without first engaging in undue experimentation.

Claim Rejections - 35 USC § 112

Claims 1-16 and 30 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising introducing a large nucleic acid molecule metabolically labeled with bromodeoxyuridine or iododeoxyuridine into cells, detecting labeled cells and measuring the product of a reporter gene encoded by the nucleic acid, does not reasonably provide enablement for the method wherein the nucleic acid is labeled by any means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In response to the rejection of record, Applicant first cites *In re Grimme et al.* 124 USPQ 449, 502 (CCPA 1960) and argues that there is no requirement for disclosure of every species within a genus (page 7). Applicant asserts that it is sufficient that the disclosure teaches one of skill in the art what the invention is and how to practice it. Applicant's point is taken; however, although the instant disclosure teaches the skilled artisan what the invention is, it does not teach how to practice the full scope of the claimed invention. In *In re Grimme et al.* the reasoning behind the Court's finding was that the claims were only generic to a closely related set of compounds. In the instant case, however, the claims are generic to a wide variety of methods of labeling nucleic acids, many of which are established to damage the nucleic acids such that they are no longer competent to express. Thus, the methods disclosed in the specification teach the skilled artisan only how to practice the claimed invention limited to labeling the nucleic acid by the method reduced to practice in Example 7 and the Declaration filed with the present amendment.

Applicant next argues that, according to *In re Marzocchi & Horton*, 58 CCPA 1069, 439f. 2D 220, 169 USPQ 367, 369-370 (1971; hereinafter *Marzocchi*), statements provided in the disclosure of a patent application are presumed to be true (page 7). However, the Office Action does not question the truthfulness of statements in the specification. At page 5, the Office Action states, "no data is provided to support this assertion, which is at odds with the teachings of the prior art, therefore it is unclear whether this is a statement of fact or a prophetic statement." Thus, the Office Action is not questioning a statement of fact, but questioning whether a statement of fact has been made. Likewise, the statements in the paragraph immediately following the sentence quoted above do not question a statement provided in the specification, but point out that no statement has in fact been made regarding the outcome of the experiments described and therefore the Examiner must infer what those results might be based on the available teachings. To the extent that the claims are limited to method comprising introducing a large nucleic acid molecule metabolically labeled with bromodeoxyuridine or iododeoxyuridine, the enablement rejection has been withdrawn in view of Applicant's clarification of the statements contained in the specification and the Declaration filed with the present amendment.

Next, Applicant discusses enablement for the instant claims in view of the criteria set forth in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) for determining the degree of permissible experimentation, which criteria were also addressed in the First Office Action.

With regard to the scope of the claims and level of skill in the art, the Examiner agrees with Applicant's characterization. The claims are directed to a method for detecting or

determining the delivery and expression of a nucleic acid introduced into a cell by introducing a labeled large nucleic acid molecule, detecting the labeled cells and measuring expression of the reporter gene product. The claims are not limited to any particular type of DNA label or method of labeling the DNA and thus encompass any method that can be used to label DNA with any type of label molecule. It should be made clear that, the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation.

It should be made clear that, the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation.

> Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification). (see *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513).

With regard to the teachings of the specification, Applicant argues that each of the steps of the claimed methods are described in the specification in detail and the specification provides working examples of particular embodiments (page 9). Applicant states, "the specification exemplifies the steps of the method in numerous working examples". With regard to the method for labeling nucleic acids, Applicant cites statements in the specification which broadly teach that labels that are directly detectable, such as radioactive labels, or indirectly detectable, such as epitope labels, are encompassed. Applicant also cites the detailed description of *in situ* metabolic labeling of artificial chromosomes with iododeoxyuridine or bromodeoxyuridine (page 10).

Applicant also cites teachings related to delivery and detection of labeled nucleic acids and for measuring expression of reporter genes (pages 10 and 11).

It must first be pointed out that, other than metabolic labeling of artificial chromosomes with bromodeoxyuridine or iododeoxyuridine, the teachings cited by Applicant are merely broad recitations of DNA labeling and delivery methods, and methods of detecting reporter gene expression. These methods are well established in the art and were available prior to publication of the art cited in the previous Office Action as a basis for the *prima facie* finding of nonenablement. It should be made clear that the issue at hand is not whether the skilled artisan would be able to label DNA, or be able to deliver DNA into a cell, or be able to measure expression of a reporter gene. The issue is whether the disclosure is enabling for claims that broadly encompass any method of labeling DNA such that the labeled DNA is both detectable when introduced into a cell and competent for detectable expression of a reporter gene. Beyond the specific teaching of the *in situ* incorporation of iododeoxyuridine or bromodeoxyuridine into artificial chromosomes, which is demonstrated in the Declaration filed with the present amendment to provide both detectable labeling and reporter gene expression, the instant disclosure provides no guidance that would enable the skilled artisan to overcome the art recognized unpredictability of obtaining transgene expression from a labeled nucleic acid molecule.

With regard to knowledge available in the art at the time of filing, Applicant cites many examples of teachings directed to delivery of nucleic acid molecules into cells (paragraph bridging pages 13-14), teachings directed to use of reporter genes (page 14, first full paragraph) and some examples of DNA labeling methods (page 14, second full paragraph). Again,

Applicant's arguments miss the point of the enablement rejection, which is the unpredictability of obtaining detectable expression of a reporter gene from a labeled DNA molecule. It is acknowledged that there are a variety of ways to label a nucleic acid and deliver that nucleic acid into cells. However, it was established in the previous Office Action that obtaining detectable expression from a nucleic acid once it is labeled is unpredictable, and it is generally the case that labeling DNA prevents transcription from the DNA (see especially bridging pages 4-5 of the previous Office Action). Therefore, even if each step in the method, when considered individually, is enabled over its full scope, the combination of steps set forth in the claims is not enabled because the labeling step interferes with the expression step. In short, the claims are not enabled because practicing the claimed invention requires expression from a labeled nucleic acid molecule.

With regard to working examples, Applicant argues that the specification provides numerous working examples and descriptions of the labeling, delivery and detection of delivered nucleic acid. Applicant specifically points to: Example 1, section B, which describes calcium phosphate transfection of cells with an unlabeled plasmid comprising a GFP reporter gene and detection of GFP expression; Example 4, which describes lipofection of cells with iododeoxyuridine-labeled DNA and detection of labeled DNA but not expression; Examples 5 and 6, which describes ultrasound mediated transfection of cells with unlabeled DNA and detection of reporter gene expression; and Example 7, which describes labeling of DNA with iododeoxyuridine or bromodeoxyuridine by incubating cells comprising the DNA to be labeled in medium comprising the labeled nucleotides, transfection of the labeled DNA into cells and measurement of beta galactosidase reporter gene expression. Thus, of the numerous working

examples cited by Applicant, only Example 7 provides all of the elements of the claimed invention and is limited to a single method of labeling DNA with two closely related nucleotide analogs. However, given the broad scope of labels and labeling methods encompassed by the claims and the unpredictability of practicing the claimed invention with any given label or method of labeling, the single working example of the claimed invention described in the specification does not demonstrate enablement for the full scope of the claimed subject matter.

With regard to predictability of the claimed invention, Applicant generally states, "[h]aving described the claimed methods and detailed the numerous agents and procedures for effecting each step in the methods in the application, there is no issue of predictability in the instant case" (page 16). Again, Applicant appears to be equating enablement for the individual method steps with enablement for the method as a whole. As pointed out above, even if one were to concede, *arguendo*, that each of the method steps is fully enabled, the rejection is based on the art recognized unpredictability of obtaining reporter gene expression from a labeled DNA, which the skilled artisan must be able to do in order to practice the claimed invention.

Regarding the art cited in the previous Office Action to support the *prima facie* finding of nonenablement, Applicant generally states that the references cited "bear little relevance to enablement of the steps of the instant methods as of their filing date" (bridging pages 12-13). This assertion seems to be based on three grounds which are repeated throughout Applicant's discussion of the references. First, Applicant asserts that the citations do not represent the state of the art at the time of filing because they were published approximately 2 years prior to the filing of the instant application. Similarly, Applicant also asserts that the teachings in the cited art do not speak to enablement for the claims of the instant application because the authors do not have

benefit of the teachings of the specification. Applicant's point is taken to the extent that the cited art does not consider *in situ* metabolic labeling of DNA using bromodeoxyuridine or iododeoxyuridine, which is demonstrated in the Declaration filed with the instant amendment to allow for detection and expression from a detectibly labeled nucleic acid. However, the instant claims are not limited to metabolic labeling of DNA using bromodeoxyuridine or iododeoxyuridine. Instead, the claims encompass any label and method of labeling DNA including those identified in the cited art as damaging to DNA and shown to prevent expression from the labeled DNA. As described in the previous Office Action, Felgner *et al.* teaches, "all of the technologies...for chemically modifying plasmid DNA result in DNA damage and interfere with its transcriptional activity"; Neves *et al.* demonstrates that reporter gene expression is greatly reduced by labeling DNA with *p*-azido-tertrafluorbenzylamido-lissamine and abolished by labeling DNA with rhodamine labeled nucleotides; and Zelphati *et al.* teaches, "the methods that have been employed to directly modify DNA either reduce or destroy its ability to be transcribed. In addition, the available approaches to chemically modify plasmid, which utilize photolysis, nick translation, or the use of chemically active nucleotide analogs, attack the DNA randomly so that the final product is chemically heterogeneous and poorly defined" (see the discussion bridging pages 4 and 5 of the previous Office Action).

Therefore, the art of record, viewed as a whole, teaches that labeling DNA generally disrupts transcription and provides several specific examples of labels and methods of labeling for which this is the case. Clearly, these teachings establish that, as of 1999, the skilled artisan in possession of any specific working embodiment of the claimed invention would not be able to extend that knowledge such that the method could be generally practiced, regardless of the label

or method of labeling used, without engaging in undue experimentation. Although Applicant asserts that the state of the art in 1999 is irrelevant to the state of the art two years later when the application was filed, Applicant does not cite a single example of a teaching from the art to support this contention.

The third basis for Applicant's generally dismissing the cited art as irrelevant to the instant invention is that the art discusses labeling and expression from plasmid DNA in the range of less than 10 Kb while the instant claims are now limited to practicing the claimed method using DNA of at least 0.5 Mb. Applicant states, "Felgner *et al.* provides no insights regarding delivery or expression of labeled nucleic acid molecules in this size range" (page 17). However, Felgner *et al.* teaches that all of the technologies for chemically modifying plasmid DNA result in *DNA damage*. Clearly, increasing the size of a nucleic acid molecule does not make it immune to damage that affects the nucleic acid itself. Applicant asserts that the instant application provides methods of labeling that do not result in breakdown of the nucleic acids. Although this point is taken with respect to *in situ* metabolic labeling of DNA with bromodeoxyuridine or iododeoxyuridine, the claims are not so limited. At least insofar as the large nucleic acid of the claims is still a nucleic acid and the instant claims encompass a method wherein DNA is labeled using chemical modification, the teachings of Felgner *et al.* are plainly relevant to the instant claimed method.

Similarly, Applicant argues that the teachings of Neves *et al.* are not relevant to the instant claims because Neves *et al.* teaches difficulties encountered in photo-activated labeling of plasmid DNA, "whereas the instant application teaches methods for measuring gene expression and delivery of large nucleic acid molecules" (page 19). Applicant asserts that the statement of

Neves *et al.* regarding inactivation of DNA by the high number of fluorescent nucleotides incorporated and by modification of plasmid structure refers "specifically to the plasmid DNA molecules disclosed in Neves *et al.* which are small and have distinct structural features relative to the large labeled nucleic acid molecules" (page 19). However, Neves *et al.* teaches problems encountered obtaining expression from a DNA molecule labeled by nick translation and photoactivation with UV light. It is unclear exactly what structural features are comprised by the large nucleic acids of the instant claims that make them immune to the problems encountered by Neves *et al.* in attempting to label DNA by nick translation or photoactivation in view of the fact that the damage induced by the enzymes used in nick translation and UV light is independent of the size of the nucleic acid. Applicant's assertion that the teachings of Neves *et al.* are irrelevant because the teachings of Neves *et al.* is limited to plasmid DNA is particularly perplexing in view of the fact that the nucleic acids of the instant claims clearly encompass plasmids, as evidenced by claim 12.

Applicant further states, "the instant application provides remedies to prevent delivery of damaged DNA and methods to increase nucleic acid stability and intactness" and "the instant application provides remedies for any deficiencies presented by Neves *et al.*" (page 19). However the teachings cited are directed to methods of detecting damage, not preventing damage, and the Examiner can find no discussion of remedies for damage created by nick translation or UV exposure. Thus, it is unclear how the teachings of the instant specification remedy any of the deficiencies presented by Neves *et al.*

With regard to the teachings of Zelphati *et al.*, Applicant again asserts that the teachings therein are irrelevant to the instant claimed methods because the nucleic acids of the claims are

much larger than the nucleic acids used by Zelphati *et al.* Applicant further contends that the working examples provide descriptions of reagents that may be used to stabilize labeled nucleic acids such as hexylene glycol, spermine and spermidine. However, Zelphati *et al.*, like Felgner *et al.* and Neves *et al.*, teaches that the methods used to label nucleic acids inhibit expression from the nucleic acids because they damage the nucleic acids themselves. Clearly, with regard to the effects of various labeling approaches on nucleic acids, the relevant feature (i.e., the nucleic acid nature) is shared by the nucleic acids of both Zelphati *et al.* and of the instant claims, while the size of the nucleic acids is, at best, a minor secondary consideration. With regard to the stabilizing agents hexylene glycol, spermine and spermidine, the specification teaches that the chemicals are "[c]ondensing agents...added to the sheath buffer to maintain condensed intact chromosome after sorting" (page 52). These stabilizing agents merely maintain the DNA in a compact state and in no way remedy the damage to DNA induced by photolysis, nick translation or chemically active nucleotide analogs described by Zelphati *et al.* (paragraph bridging pages 15-16).

Applicant next asserts that the teachings of Zelphati *et al.* have been mischaracterized. Applicant states, "[w]hile Zelphati *et al.* may summarize pitfalls of particular techniques as they pertain to plasmid DNAs, the authors go on to provide a peptide nucleic acid labeling method for small plasmid DNA molecules that permits gene expression at a level similar to unmodified plasmid DNA" (page 22). First, it is unclear in what way the teachings of Zelphati *et al.* have been mischaracterized when it is the "pitfalls of particular techniques", which Applicant acknowledges, that form the basis of the enablement rejection. It must again be made clear that the instant claims are not limited to any particular label or labeling method and therefore

encompass the methods that Zelphati *et al.* indicates are inadequate for use in the claimed invention. It is true that Zelphati *et al.* describes an enabled method, however the method disclosed by Zelphati *et al.* is not enabling for the broad scope of the instant claims.

Next, Applicant asserts that the Office Action has erroneously equated "limitations" with "unpredictability". Applicant submits, "although certain methods of labeling nucleic acid molecules can be associated with certain limitations in gene expression, this does not establish the art as unpredictable. The issue of whether the specific instant claims are enabled by the specification should not turn on the specific limitations previously encountered in measuring delivery and expression of labeled nucleic acids. Rather the relevant question with regard to enablement of the subject matter of the instant claims is whether the particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use then invention" (page 22).

By this, Applicant appears to be arguing that the problems encountered in practicing methods similar to the claimed invention do not suggest unpredictability in the art. To clarify, unpredictability, as it pertains to the instant case, concerns the probability that the teachings set forth in the specification would enable the skilled artisan to practice the full scope of the claimed invention without undue experimentation. The instant claims encompass a method wherein a nucleic acid is labeled with *any* molecule and by *any* means, while instant specification provides a single working example of the claimed method. Thus, it must be determined whether the teachings in the art and specification would enable the skilled artisan to extend the teachings therein such that the full scope of the claimed invention can be practiced without undue experimentation. Clearly, the "limitations", which Applicant appears to acknowledge exist in the

art, indicate that there are many barriers to obtaining useful expression from a labeled nucleic acid molecule. Further, the art provides no means to overcome these barriers short of random trial and error experimentation. It is recognized in patent law that the presence of inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled. "The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414). However, *Atlas* also provides, "[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). In the instant case, the art teaches that methods commonly used to label nucleic acids disrupt expression. Neither the art nor the instant specification provide teachings that would enable the skilled artisan to practice the claimed invention as it broadly encompasses any label or method of labeling nucleic acids or identify those embodiments that are enabled without undue trial and error experimentation.

Thus, for reasons of record in the previous Office Action and herein above, the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement for the full scope of the claimed subject matter.

Claim Rejections - 35 USC § 35 U.S.C. §103

Claims 1-4 and 11-15 were rejected under 35 U.S.C. 103(a) as unpatentable over either one of Felgner *et al.* (*supra*) or Zelphati *et al.* (*Supra*) in view of Nolan *et al.* (2000) WO 00/34436.

Applicant first traverses the rejection on the grounds that none of the references teach or suggest a method for monitoring/measuring delivery and expression of large labeled nucleic acids (see especially the second full paragraph on page 39). Applicant states, "[t]he claims of the present method are directed to the steps of: introducing labelled large nucleic acid molecules that encode a reporter gene into cells; detecting labelled cells as an indication of delivery of the nucleic acid into the cell; and measuring the product of the reporter gene. The combination of teachings of the [sic] references cited must provide all of these steps, not just the single step of introducing fluorescently labelled nucleic acid" (page 39). This argument has been fully considered but is not found persuasive because it appears to be based on a piecemeal analysis of the art. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As pointed out in the previous Office Action, Felgner *et al.* and Zelphati *et al*, each teach a method for detecting or determining delivery and expression of a nucleic acid introduced into a cell comprising: introducing labeled nucleic acid molecules that encode a reporter gene into cells; detecting labeled cells as an indication of delivery of the nucleic acid onto a cell; and measuring the product of the reporter gene. Nolan *et al.* teaches a method of delivering large DNA into cells wherein the DNA is fluorescently labeled. Thus, the art teaches all of the

limitations of the claims and, for reasons of record, provides motivation to combine the teachings of the art. Thus, the invention as a whole is obvious in view of the teachings of the prior art.

Next, Applicant argues that the method of Felgner *et al.* and Zelphati *et al.* would be incompatible with the method of Nolan *et al.* because Nolan *et al.* teaches a method of introducing a single fluorescent chromosome into a cell while the method of Zelphati *et al.* and Felgner *et al.* is "designed to operate with many thousands of copies of plasmid to monitor gene expression" (first full paragraph on page 40). This argument is not found persuasive because it mischaracterizes the teachings of Zelphati *et al.* The passage cited by Applicant for support has to do with experiments to determine stability of plasmid DNA and trafficking of labeled DNA to the nucleus. Zelphati *et al.* estimate 30,000-50,000 copies of plasmid per cell 24 hours after transfection. However, Zelphati *et al.* in no way conclude that this number is the minimum requirement to detect delivery or expression from a labeled plasmid. This is clearly evidenced by the fact that Zelphati *et al.* demonstrate detectable fluorescence at 3 hours after transfection, at which point one would expect the plasmid copy number to be much less than at 24 hours. Furthermore, the skilled artisan would know that fluorescence from the large DNAs taught by Nolan *et al.* could be readily increased by simply increasing the number of PNA binding sites (and therefore labeled PNAs) incorporated in the DNA. Thus, the skilled artisan would not conclude, based on the teachings of Zelphati *et al.*, that the method taught by Nolan *et al.* is incompatible with the methods of Zelphati *et al.* and Felgner *et al.* and would have a reasonable expectation of success in combining the methods.

Next, Applicant argues that, Nolan *et al.* provides no teaching or suggestion that there is a need for monitoring gene expression nor measuring gene expression along with DNA delivery as

set forth in the instantly claimed methods and therefore does not cure the deficiencies of Felgner *et al.* or Zelphati *et al.* First, this again appears to be a piecemeal analysis of the references because Felgner *et al.* and Zelphati *et al.* both teach monitoring gene expression. Therefore, Felgner *et al.* and Zelphati *et al.* are not, in fact, deficient in the teaching of monitoring gene expression. Next, even though Nolan *et al.* does not explicitly teach monitoring gene expression, Nolan *et al.* states that the method is to be used to deliver chromosomes that carry any genetic sequence for commercial or clinical relevance, and emphasizes gene therapy and transgenic animal technologies (see especially the second paragraph on page 1). Further, the instant reporter gene, as it is defined in the third full paragraph on page 16, encompasses any gene that expresses a detectable gene product. As it is routine in the art to measure expression of a gene of interest in processes such as gene therapy and transgenic animal protocols in order to verify that a functional copy of the transferred gene has in fact been taken up by the cell, measuring expression would be obvious to one of ordinary skill in the art.

Next, Applicant argues that there is no teaching or suggestion in Felgner *et al.* or Zelphati *et al.* that the labeling method is suitable for large nucleic acids or how PNA may be used with large nucleic acid molecules. This argument is not found persuasive because the method of Felgner *et al.* or Zelphati *et al.* requires only the incorporation of PNA binding sites into the nucleic acid sequence of the target DNA and then hybridizing a labeled PNA (see especially Figure 1 and the caption thereto). As Nolan *et al.* teaches the delivery of custom designed mammalian chromosomes (see especially page 1, lines 9-10) it would be obvious to one of ordinary skill that the labeling method of Felgner *et al.* or Zelphati *et al.* could be adapted for use with the "designer chromosomes" of Nolan *et al.* by simply including PNA binding sites.

Applicant suggests that limitations such as that PNAs can inhibit gene expression, block restriction enzyme activity or act as an artificial promoter would prevent the skilled artisan from using PNAs with large DNAs. However, there is nothing to suggest that any of these would be more problematic with large DNAs than with smaller plasmids, and Felgner *et al.* and Zelphati *et al.* clearly demonstrate that PNAs can be used to label plasmid DNA without inhibiting gene expression. Furthermore, the skilled artisan would know to locate the PNA binding sites away from important restriction sites and sequences that might be problematic were they to be expressed ectopically. Applicant also cites teachings from Zelphati *et al.* indicating that PNAs can inhibit translation, transcription and telomerase activity. However, it should first be pointed out that this teaching is presented as evidence that these processes are not likely to cause dissociation of the PNA from the nucleic acid and clearly do not prevent the successful application of the disclosed technology as evidenced by the successful application using plasmid DNA. Again, Applicant has provided no reason to believe that the large DNAs taught by Nolan *et al.* are substantially different from the smaller DNAs of Felgner *et al.* and Zelphati *et al.* with respect to the successful application of PNA labeling.

Finally, Applicant argues that the rejection is based on improper use of hindsight. Citing *In re Laskowski*, Applicant argues, "the disclosure of the Applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed" (page 43). This argument has been fully considered but is not found persuasive. It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge

gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicant seems to be arguing that it is improper for the examiner to use the claim limitations in a search of the prior art, or perhaps that it is improper to combine teachings from the prior art according to the limitations of the claims. The finding in *In re Laskowski* was based on the fact that a critical element of the claimed invention was not disclosed in the prior art. In contrast, as described in the previous Office Action and herein above, all of the elements of the instant claimed invention are disclosed in the prior art and analysis of the teachings set forth in the cited work according to the factual inquiries of *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), establish that it would be obvious to combine the teachings to produce the instant claimed invention. Therefore, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms

JAMES KETTER
PRIMARY EXAMINER